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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/071,541	05/04/98	HUANG H	040750-5001

HM12/0217

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EXAMINER	
FONDA, K	

ART UNIT	PAPER NUMBER
1623	8

DATE MAILED: 02/17/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12-23-99.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-16 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

Applicant is advised that should claims 9-12 be found allowable, claims 13-16 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Although claims 9-12 recite a pharmaceutical composition, while claims 13-16 recite a kit for treating cancer, the components of the composition do not differ from those of the kit. Thus the claims are substantially duplicative.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 lacks positive antecedent basis for "the apoptosis-inhibiting effect" and for "the step", and is therefore indefinite.

Claims 7, 11, and 15 are indefinite because the phrase "relatively selective" has no particular art-recognized meaning, and has not been adequately defined in the specification.

Claims 8, 12, and 16 are indefinite because the phrase "its derivatives" has no particular art-recognized meaning, and has not been adequately defined in the specification.

Claims 9 and 13 lack positive antecedent basis for "the resistance", "the induction", and "the increased rate" and are therefore indefinite.

Claims 9 and 13 are furthermore indefinite because they do not state what it is that targets the recited "target cell or tissue". Applicant will note that claim 1 is not subject to this rejection because claim 1 states "a target cell or tissue of a mutant EGFR gene".

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over HAN *et al.* (K) in view of REED (A).

Applicant claims a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a tyrosine kinase inhibitor to the cell or tissue, in combination with a therapy which is effective to induce apoptosis or increase the rate of apoptosis. The mutant EGFR gene may be ΔEGFR. The cell or tissue may be a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian cancer. The therapy effective to induce apoptosis or increase the rate of apoptosis may be administration of cisplatin, paclitaxel, or vincristine. The tyrosine kinase inhibitor may be tyrphostin AG1478.

Applicant also claims a pharmaceutical composition and a kit for treating cancer comprising (A) an amount of an agent which is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue, and (B) an amount of a tyrosine kinase inhibitor effective to reduce resistance mediated by a mutant EGFR to induction of apoptosis or to increased rate of apoptosis in a target cell or tissue. The agent may be cisplatin, paclitaxel, or vincristine. The tyrosine kinase inhibitor may be tyrphostin AG1478.

HAN teaches that tyrphostin AG1478 is a tyrosine kinase inhibitor that preferentially inhibits human glioma cells expressing the mutant ΔEGFR rather than wild-type EGFR; see the abstract. Additionally, HAN suggests that because tyrphostin AG1478 is a relatively specific inhibitor of ΔEGFR, it may be therapeutically useful with regard to glioblastomas, and breast, lung, and ovarian cancers, because the ΔEGFR mutation occurs frequently in these cancers; see the abstract and the last two paragraphs on page 3861. HAN does not state that a tyrosine kinase inhibitor such as tyrphostin AG1478 should be administered together with a therapy which is effective to induce apoptosis or increase the rate of apoptosis.

REED teaches that cisplatin, taxol (also known as paclitaxel), and vincristine are known cancer chemotherapeutic

agents which have in common an ability to induce apoptosis in cancer cells; see column 22, lines 4-15.

It would have been obvious for a person of ordinary skill in the art at the time of the invention to provide a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a tyrosine kinase inhibitor to the cell or tissue, in combination with a therapy which is effective to induce apoptosis or increase the rate of apoptosis, wherein the mutant EGFR gene is ΔEGFR; the cell or tissue is a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian cancer; the therapy effective to induce apoptosis or increase the rate of apoptosis is administration of cisplatin, paclitaxel, or vincristine; and the tyrosine kinase inhibitor is tyrphostin AG1478. An ordinarily skilled worker would have been motivated to do so in order to obtain the expected combination of therapeutic benefits with regard to cancer treatment. HAN had clearly suggested that use of tyrphostin AG1478 for treatment of glioblastomas, and breast, lung, and ovarian cancers. As taught by REED, cisplatin, taxol (also known as paclitaxel), and vincristine were known cancer chemotherapeutic agents which could induce apoptosis in cancer cells. Because tyrphostin AG1478 had been taught by HAN to be a relatively specific inhibitor of ΔEGFR, an ordinarily skilled worker would have expected the

claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of ΔEGFR, in accordance with the instant method claims.

It would furthermore have been obvious to provide a pharmaceutical composition or kit for treating cancer comprising (A) an amount of an agent which is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue, and (B) an amount of a tyrosine kinase inhibitor effective to reduce resistance mediated by a mutant EGFR to induction of apoptosis or to increased rate of apoptosis in a target cell or tissue, wherein the agent is cisplatin, paclitaxel, or vincristine; and the tyrosine kinase inhibitor is tyrphostin AG1478. An ordinarily skilled worker would have been motivated to do so in order to provide a therapeutically useful composition or kit to be used in cancer treatment (see the Examiner's explanation of obviousness of the method in the previous paragraph), which would enhance compliance with an appropriate treatment regimen, as well as provide added convenience for both clinician and patient.

Applicant is reminded that it is well established that no patentable invention resides in combining old ingredients of known characteristics where the results obtained thereby are no more than the additive effects of the ingredients. See *In re Sussman*, 1943 C.D. 518; *In re Huellmantel*, 139 USPQ 496; and *In re Crockett et al.*, 1266 USPQ 186. Also, it is obvious to

combine ingredients which have been separately employed for a given purpose in order to obtain the expected combination of benefits. See *In re Greenfield*, 571 F.2d. 1185, 197 USPQ 227 (CCPA 1978). In the instant case, there has been no clear and convincing showing (see I*n re Lohr et al.*, 137 USPQ 548), commensurate in scope with the claims (see *In re Lindner*, 173 USPQ 356; *In re Hyson*, 172 USPQ 339, and *In re Boesch et al.*, 205 USPQ 215 (CCPA 1980)), of any unexpected results.

The following reference, which discloses in the abstract that certain inhibitors of protein tyrosine kinase are useful for treating cancer, is cited to indicate the state of the art at the time of the invention more completely: Blankley *et al.* (B).

An initialed copy of the supplemental IDS submitted 04-30-99 is enclosed. An initialed copy of the IDS submitted 04-14-99 is also enclosed. The Examiner has obtained and considered the U.S. patent documents cited therein. However, the non-patent documents cited therein have not been considered because no copies were present in the file when it was received by the Examiner. Applicant is advised that if Applicant submits these non-patent documents together with a new IDS form and evidence (for example, a stamped receipt postcard) of their original

submission on 04-14-99, they will be considered by the Examiner as if they had been present in the file at the time of the first action on the merits.

No claim is allowed.

Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The number of the fax machine for official papers in Technology Center 1600 is (703) 308-4556. Any document submitted by facsimile transmission will be considered an official communication unless the cover sheet clearly indicates that it is an informal communication.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kathleen Kahler Fonda, at telephone number (703) 308-1620. Examiner Fonda can generally be reached from Tuesday through Friday, as well as on alternate Mondays, between 7:30 a.m. and 5:00 p.m. If the Examiner cannot be reached, questions may be addressed to Supervisory Patent Examiner Marian Knode at (703) 308-4311. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Kathleen Kahler Fonda

Kathleen Kahler Fonda, Ph.D.
Primary Examiner
Art Unit 1623